OsteoArthritis and Cartilage (2006) **14,** 1111–1118

doi:10.1016/j.joca.2006.05.004

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

An analgesic model for assessment of acute pain response in osteoarthritis of the knee[1]

R. W. Moskowitz M.D.†‖*, A. Sunshine M.D.‡§, M. Hooper M.D., M.S.†, N. Z. Olson M.P.S.§ and G. D. Cawkwell M.D., Ph.D.‖

† *Department of Medicine, Case Western Reserve University School of Medicine and University Hospitals, Cleveland, OH, USA*

‡ *New York University School of Medicine, New York, NY, USA*

§ *Analgesic Development Ltd., New York, NY, USA*

‖ *Pfizer Global Pharmaceuticals, New York, NY, USA*

Summary

Background: Osteoarthritis (OA) is frequently treated only during periods of flare, in which rapid onset of analgesia is the outcome target.

Objective: To assess an acute pain model of knee OA in flare.

Methods: In a multicenter, randomized, double-blind, controlled study, 530 patients aged ≥50 years received valdecoxib 10 mg qd ($n = 212$), rofecoxib 25 mg qd ($n = 208$), or placebo ($n = 110$). Pain intensity (PI) was measured on a visual analog scale (VAS) at baseline after a 10-min walk. Patients took their first dose of study medication, rested for 20 min, then measured their PI VAS at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h, each time following a 10-min walk.

Results: PI VAS differences (PID) were significantly greater vs placebo both with valdecoxib and rofecoxib ($P < 0.05$) beginning as early as 3 h (intent-to-treat population). The percentage of patients with analgesia onset from 4 h was significantly higher with both valdecoxib (55%) and rofecoxib (56%) relative to placebo (40%). Median time to first onset of analgesic was shorter with both valdecoxib and rofecoxib compared with placebo ($P = 0.104$ vs valdecoxib; $P = 0.036$ vs rofecoxib).

Conclusions: This acute pain model of knee OA flare detected significant pain relief with agents known to relieve pain in OA and placebo within hours after the first treatment dose, allowing assessment of pain relief within hours rather than days or weeks when evaluating analgesic efficacy in OA. This model is undergoing further study to determine optimal walk times, distances, and rates to maximize its sensitivity.

Key words: Valdecoxib, Osteoarthritis, COX-2 inhibitor, Acute pain model.

Introduction

Osteoarthritis (OA) symptoms are episodic, and the disease is frequently treated only during periods of flare. On average, patients with OA are treated for only 94 days per year[1]. Most traditional studies involving OA patients measure efficacy after several weeks to months of treatment. In patients experiencing a flare of painful symptoms, rapid onset of pain relief would be advantageous; accordingly, it would be useful to measure the onset of analgesic action shortly following medication. A rapid onset of analgesia in patients with OA flare may help to limit worsening of chronic pain resulting from peripheral and central sensitization[2].

We have modified an analgesic model, which assesses the onset of analgesia in patients experiencing an OA flare of the knee[3]. In this model, treatment is initiated following a period of induced pain (flare) to evaluate acute pain response. Pain intensity (PI) is assessed using the visual analog scale (VAS) during the first 6 h following medication. Each pain assessment is made following a 10-min walk to more closely simulate the clinically relevant pain that is characteristically seen in patients with OA.

In previous acute pain studies, following dental extraction categorical mean PI difference (PID) and pain relief scores were similarly significantly improved vs placebo with valdecoxib 40 mg, and with an oxycodone 10 mg/acetaminophen 1000 mg combination[4]. In another dental pain model study, median time to onset in responders following a valdecoxib dose of 10 mg was 39 min, statistically significantly different from placebo[5]. Significantly improved PID scores and pain relief scores with rofecoxib 50 mg vs placebo were achieved 45 min after the first dose[6,7]. There is currently no published information comparing valdecoxib 10 mg with rofecoxib 25 mg in OA patients, or assessing onset of analgesia following medication on day 1 in patients with OA in flare, using PI after walking.

[1]The study was sponsored by Pfizer Global Pharmaceuticals and Pharmacia Corporation.

*Address correspondence and reprint requests to: Roland W. Moskowitz, M.D., Professor of Medicine, Department of Medicine, Case Western Reserve University School of Medicine and University Hospitals, 3609 Park East Drive, Suite 307N, Cleveland, OH 44122, USA. Tel: 1-216-591-1443; Fax: 1-216-591-1354; E-mail: roland.moskowitz@uhhs.com

Received 24 November 2005; revision accepted 9 May 2006.

The analgesic OA flare model was assessed in two identically designed studies comprised of a 24-h flare model assessment phase, and a 2-week extension, which compared treatment with the cyclooxygenase (COX)-2 specific inhibitors, valdecoxib and rofecoxib, and placebo. Although valdecoxib is approved for the relief of signs and symptoms of OA[6–10], the United States Food and Drug Administration, in April 2005, requested that the manufacturer (Pfizer, Inc.) suspend sales of valdecoxib, due primarily to an increased risk of rare, but potentially severe cutaneous adverse reactions[11]. Rofecoxib, also indicated for the relief of the signs and symptoms of OA, was withdrawn from the market voluntarily by its manufacturer due to concerns regarding cardiovascular risk. Patients with knee OA flare were randomized to receive their first dose of double-blind treatment with valdecoxib 10 mg, rofecoxib 25 mg, or placebo. Onset of analgesia was measured in the flare model assessment during the first 6 h, following a series of 10-min walks. In study 1, the OA flare model failed to show any treatment differences vs placebo on day 1; this may have been a result of differing levels of familiarity and application of the newly designed study methodology in some of the investigative sites. This paper, which focuses on the flare model methodology, presents the detailed results observed in study 2 utilizing the modified analgesic model.

Methods

The protocol for this multicenter, randomized, double-blind, double-dummy, placebo-controlled study was reviewed by the appropriate Institutional Review Boards, and all patients provided written informed consent before entering the study. The trial was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

PATIENTS

Patients were aged at least 45 years, and had OA of the knee according to the American College of Rheumatology criteria[12]. They were required to have a Functional Capacity Classification between I and III at the screening assessment[13]. In patients with bilateral knee OA, the knee with the most severe symptoms was defined as their index joint.

Eligible patients had OA in a flare state at the baseline assessment. Two categories of flare were described. Patients who had previously been receiving nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesic therapy for their OA (Category 1 patients) discontinued their treatment for at least 2 days or a minimum of five half-lives of the agent, whichever was greater, prior to the baseline visit. An OA flare state was defined as a patient's and physician's global assessment of arthritis activity of "fair", "poor", or "very poor" at the baseline visit; one subject was rated "good" at baseline. In addition, patients were required to have $\geq$3 of the following four criteria when comparing screening to baseline: patient's assessment of arthritis pain VAS walking on a flat surface at baseline of $\geq$40 mm; an increase of $\geq$2 points in Lequesne OA severity index, a validated algofunctional assessment instrument[14]; an increase of $\geq$1 grade in the patient's global assessment of arthritis; and an increase of $\geq$1 grade in the physician's global assessment of arthritis. In patients who had not previously been receiving NSAID or analgesic therapy and whose OA was not controlled (Category 2 patients), an OA flare state was defined as having $\geq$3 of the following four criteria during the baseline visit: patient's assessment of arthritis pain VAS of $\geq$40 mm; a Lequesne OA severity index of $\geq$7; patient's global assessment of arthritis of "poor" or "very poor"; and physician's global assessment of arthritis of "poor" or "very poor".

Patients were excluded from the trial if they

(1) Had been diagnosed with inflammatory arthritis or acute joint trauma of the index joint;
(2) Had a history of malignancy, active gastrointestinal disease, chronic or acute renal/hepatic disorders, or significant coagulation disorders;
(3) Had abnormal screening laboratory values exceeding 1.5 times the upper limit of normal for either aspartate aminotransferase or alanine aminotransferase, a serum creatinine $\geq$2.0 mg/dL, or any other clinically significant laboratory abnormality within 14 days prior to the baseline visit;
(4) Had received oral, intramuscular, or intra-articular corticosteroids within 8 weeks, or intra-articular hyaluronic acid in the index joint within 6 months of study drug administration;
(5) Had taken anticoagulants, NSAIDs, COX-2 specific inhibitors, or analgesic agents. However, patients were allowed to use acetaminophen (1000 mg prn, up to 4 g/day) as rescue analgesia up until 24 h before each arthritis assessment.
(6) Had taken methotrexate, gold salts, penicillamine, antimalarials, sulfasalazine, azathioprine, cyclosporine, leflunomide, etanercept, or infliximab during the screening period. Glucosamine or chondroitin sulfate was prohibited during the screening period unless the patient had been on a stable dose for at least 3 months before enrolling in the study.

Patients taking low-dose aspirin ($\leq$325 mg/day) for nonarthritic reasons were allowed to continue their aspirin regimen for the duration of the study. Antiplatelet agents, such as clopidrogel or ticlopidine, were permitted for patients on a stable dose for at least 30 days prior to the screening visit.

SCREENING ASSESSMENTS

At a screening visit between day 14 and day 0, OA assessments were taken. In the assessment of the primary outcome, "Pain in the Index Knee", patients evaluated their pain on a 100-mm VAS, where 0 = no pain and 100 = most severe pain, in response to the question, "How much pain are you having because of the OA in your index knee?"

ASSESSMENT

Baseline OA assessments on day 1

OA assessments were taken at baseline, and an assessment of flare was made, as defined above, to determine eligibility for enrollment into the study. The Western Ontario and McMaster Universities OA Index (WOMAC), a self-administered patient questionnaire, was used prior to any other OA assessments, and evaluated patients' ability to perform daily activities based on their physical function, pain, and stiffness[15]. WOMAC total domain scores using a Likert scale range from 0 to 96, pain scores range from 0 to 20, stiffness scores range from 0 to 8, and physical function scores range from 0 to 68. For each WOMAC OA Index, lower scores were considered to be better.

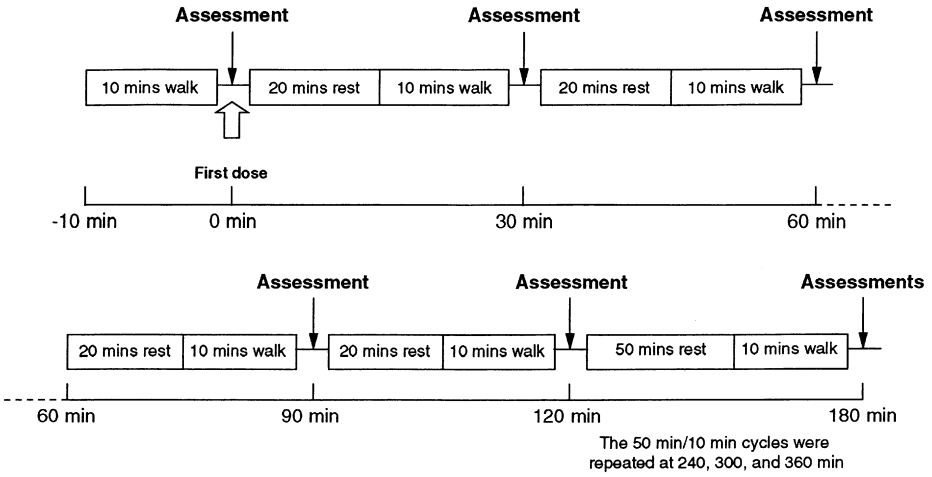

Fig. 1. Schedule of PI assessments in the clinic.

Measurement of onset of analgesia with walking on day 1

Eligible patients with OA flare of the knee were randomized 2:2:1 in the order that they were enrolled to receive their first dose of valdecoxib 10 mg, rofecoxib 25 mg, or placebo in a double-blind, double-dummy design. Patients were asked to walk on a flat surface for 10 min, after which they assessed their baseline PI VAS and took their first dose of study medication (time 0) (Fig. 1). Patients rested for 20 min, then completed the patient's assessment of OA pain VAS at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after study drug administration, each time following a 10-min walk.

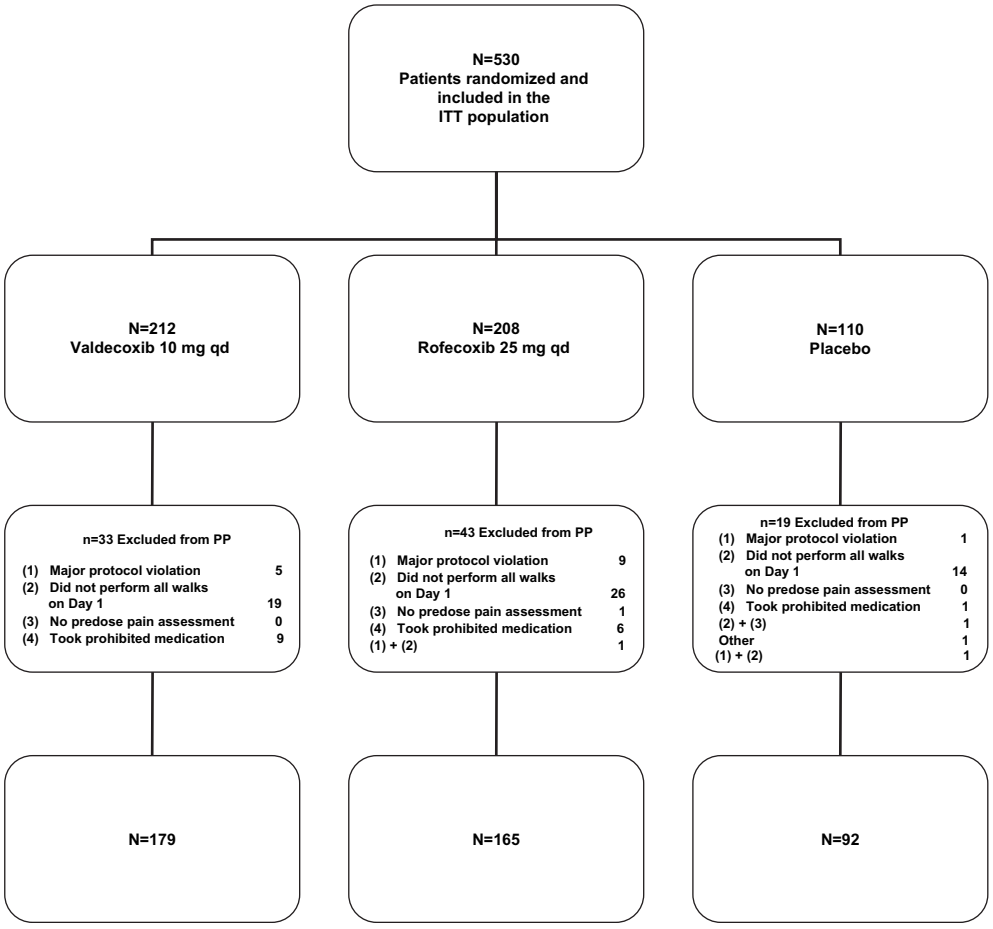

Fig. 2. Patient disposition.

Efficacy end points and statistical analyses on day 1

Two secondary efficacy end points were measured on day 1. Time-specific PID VAS scores were derived by subtracting PI scores at 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after the first dose of study drug administration from the baseline PI score, represented by pain after the first 10-min walk. Summed PID VAS at 6 h (SPID-6) was calculated from the area under the time−effect PID curve using the trapezoidal rule.

Onset of analgesia (with walking) was defined as a 25% reduction in PI from baseline. In a post hoc analysis, the time-specific incidence of the above-defined analgesic onset at 1, 2, 3, 4, 5, and 6 h after the first dose of study medication was derived for each treatment group using post hoc logistic regression analysis. In addition, the median time to first onset of analgesia was determined for each treatment group by the Kaplan Meier estimate.

The intent-to-treat (ITT) cohort contained patients who were randomized and received at least one dose of study medication. The assessable population for the onset of analgesia end points, designated as PP (per protocol) cohort, was used to analyze PID scores, SPID-6, the time-specific incidence of onset of analgesia with walking, and median time to first onset of analgesia. Specifically, the PP population contained patients in the ITT population who completed each of the required 10 ± 1 min walks before each PI assessment on day 1. In addition, the PP population contained patients in the ITT cohort who had no major preexisting protocol violations, completed a predose PI assessment, and had not taken any prohibited medications on day 1.

Results

PATIENT DISPOSITION

Patient disposition is summarized in Fig. 2. In total, 530 patients were randomized to receive valdecoxib 10 mg qd ($n = 212$), rofecoxib 25 mg qd ($n = 208$), or placebo ($n = 110$). All patients who were randomized received at least one dose of study medication, and were, therefore, included in the ITT population.

The PP cohort (assessable for onset of analgesia end points on day 1) included 435 patients (179 valdecoxib-, 165 rofecoxib-, and 91 placebo-treated patients). A total of 95 patients were excluded from the PP population for one or more reasons (Fig. 2). Most of these patients (62/95 [65%]) were excluded because they did not complete all of the 10 ± 1 min walks before each PI VAS assessment on day 1. Other reasons for exclusion were major preexisting protocol violation (17/95 [18%]), prohibited medication taken on day 1 (16/95 [17%]), no predose PI assessment (2/95 [2%]), and no informed consent form (1/95 [1%]).

There were no significant differences between treatment groups with respect to baseline patient demographics or OA assessments at screening (Table I). Patients' mean age was 63−65 years, and the mean duration of OA was 7.5−8.1 years (Table I). The percent of patients taking low-dose aspirin was similar in patients taking valdecoxib ($n = 38/212$, 17.9%), rofecoxib ($n = 49/208$, 23.6%), and placebo ($n = 26/110$, 23.6%).

Table I
Baseline demographics and OA assessments at screening of all patients

	Valdecoxib, 10 mg qd ($n = 212$)	Rofecoxib, 25 mg qd ($n = 208$)	Placebo ($n = 110$)	*P* value
Age, years				0.33
Mean (SD)	63.3 (8.9)	64.6 (9.4)	63.9 (9.2)	
Range	50−91	49−93	50−83	
Female, *n* (%)	133 (63)	137 (66)	73 (66)	0.74
Race, *n* (%)				0.95
Caucasian	159 (75)	155 (75)	84 (76)	
Black	42 (20)	47 (23)	22 (20)	
Asian	3 (1.4)	1 (0.5)	0	
Other	8 (3.8)	5 (2.4)	4 (3.6)	
Duration of OA, years				0.68
Mean (SD)	8.1 (7.7)	8.1 (8.1)	7.5 (7.0)	
Functional capacity, *n* (%)*				0.91
Class I	6 (3)	9 (4)	3 (3)	
Class II	185 (87)	176 (85)	95 (86)	
Class III	21 (10)	23 (11)	12 (11)	
OA flare category, *n* (%)†				0.33
Category 1	172 (81)	178 (86)	88 (80)	
Category 2	40 (19)	30 (14)	22 (20)	
Prescreening OA NSAIDs/ analgesics taken, *n* (%)				0.64
None	38 (17.9)	32 (15.4)	21 (19.1)	
Nonspecific NSAIDs	68 (32.1)	93 (44.7)	35 (31.8)	
COX-2 specific inhibitors	84 (39.6)	69 (33.2)	34 (30.9)	
Analgesic agents	53 (25.0)	50 (24.0)	41 (37.3)	

*Class I: Complete functional capacity with ability to carry on all usual duties without handicaps; Class II: functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints; Class III: functional capacity adequate to perform only few or none of the duties of usual occupation or self-care.

†Category 1: Patients were previously receiving NSAIDs or analgesic therapy for their OA; Category 2: patients' OA was not controlled and they were not previously receiving any OA treatment.

Table II
OA symptoms of all randomized patients during the period of flare

	Valdecoxib, 10 mg qd ($n = 212$)	Rofecoxib, 25 mg qd ($n = 208$)	Placebo ($n = 110$)	*P* value
Patient's assessment of OA pain VAS, mean (SD), mm				
Screening	52.3 (23.8)	52.5 (23.0)	55.2 (22.0)	0.48
Baseline	71.8 (16.4)	70.9 (17.0)	73.7 (16.0)	0.18
Lequesne OA severity index (range 0–24)				
Screening	12.7 (3.3)	12.8 (3.6)	12.9 (3.6)	0.83
Baseline	15.3 (3.3)	15.3 (3.2)	15.4 (3.5)	0.92
Patients' global assessment of arthritis (%)				
Screening:				0.96
Good/very good	58 (27)	57 (27)	29 (26)	
Fair	114 (54)	112 (54)	62 (56)	
Poor/very poor	40 (18)	39 (19)	19 (18)	
Baseline:				0.73
Good/very good	0	0	0	
Fair	57 (27)	60 (29)	34 (31)	
Poor/very poor	155 (73)	148 (71)	76 (69)	
Physicians' global assessment of arthritis (%)				
Screening:				0.54
Good/very good	59 (27)	61 (29)	24 (22)	
Fair	127 (60)	128 (62)	76 (69)	
Poor/very poor	26 (12)	19 (9)	10 (9)	
Baseline:				0.80
Good/very good	0	1 (<1)	0	
Fair	63 (30)	65 (31)	31 (28)	
Poor/very poor	149 (70)	142 (68)	79 (72)	

OA flare at baseline

During the period between screening and baseline, patients experienced a marked increase in the severity of their OA symptoms, with no significant differences observed among the treatment groups (Table II). Patients' assessment of OA pain VAS increased markedly across treatment groups from means of 52–55 mm at screening, to means of 71–74 mm at baseline (Fig. 3; Table II). Modified OA severity index increased on the 0–24 scale from 13 at screening to 15 at baseline.

At the screening assessment, 26–27% of patients rated their global disease assessment as good or very good. After discontinuing NSAID or analgesic agents, none of the patients rated their disease as good or very good at baseline. The percentage of patients who rated their disease as poor or very poor increased markedly from screening (18–19%) to the baseline assessment (69–73%). Results for the physicians' global assessment of OA disease at screening and baseline matched those of the patients' assessment (Table II).

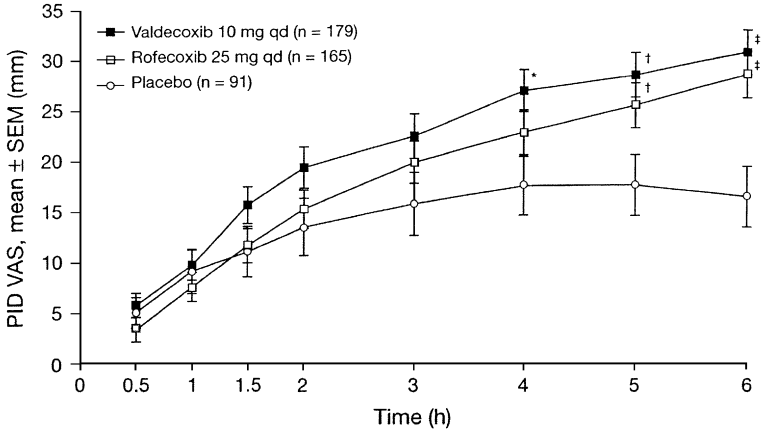

Fig. 3. Time-specific PID VAS on day 1 in the PP1 population. $^*P \leq 0.05$, $\dagger P < 0.01$, $\ddagger P < 0.001$ vs placebo.

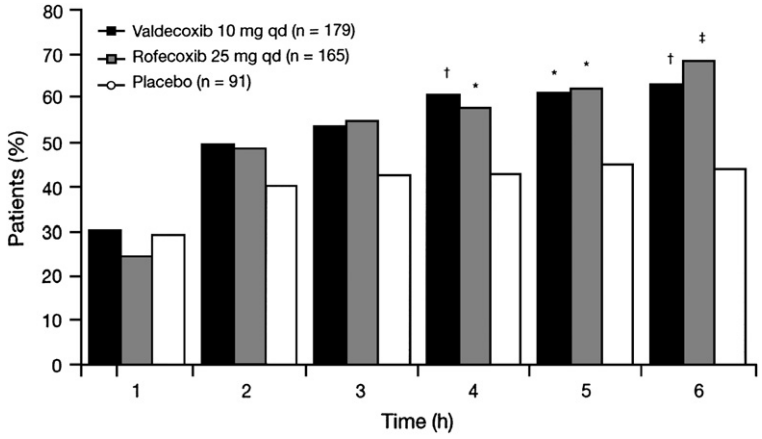

Fig. 4. Time-specific incidence of onset of analgesia, defined as a 25% PI reduction from baseline, during the first 6 h in the PP population. $^{*}P \leq 0.05$, $\dagger P < 0.01$, $\ddagger P < 0.001$ vs placebo.

ONSET OF ANALGESIA WITH WALKING

In the PP cohort, PID VAS scores were significantly greater with both active treatments vs placebo beginning at 4 h with valdecoxib, and 5 h with rofecoxib ($P \leq 0.05$) (Fig. 3).

Figure 4 shows the time-specific incidence of all patients with respect to onset of analgesia (i.e., 25% reduction in PI) from 1 to 6 h after the first dose of study medication in the PP population. By 4 h, the percentage of patients with analgesic onset was significantly higher in both valdecoxib (60%) and rofecoxib (57%) groups compared with placebo (42%; $P = 0.008$ vs valdecoxib; $P = 0.028$ vs rofecoxib). The median time to first onset of analgesia in the PP cohort was significantly shorter for both valdecoxib (2 h; 95% Confidence Interval (CI) 2.0, 3.0) and rofecoxib (2 h; 95% CI): 2.0, 3.0) compared with placebo (4 h; 95% CI: 2.0, 6 h; $P = 0.088$ vs valdecoxib; $P = 0.075$ vs rofecoxib).

Valdecoxib provided a significantly improved SPID score in the first 6 h in the PP cohort, compared with that seen in the placebo group (122.4 ± 10.3 vs 81.0 ± 14.4; $P < 0.05$). In contrast, the SPID-6 score in rofecoxib-treated patients was not significantly different from that seen with placebo (104.5 ± 10.1 vs 81.0 ± 14.4; $P = 0.098$). The difference in SPID-6 between valdecoxib and rofecoxib, however, was not statistically significant.

The analgesic onset results with the PP cohort are supported by the ITT population. Compared with placebo, PID VAS scores were significantly greater from 3 h with both valdecoxib and rofecoxib ($P < 0.05$) (Table III).

Table III
Time-specific PID VAS on day 1 in the ITT population, mean ± Standard Error of the Mean (S.E.M.)

Time (h)	Valdecoxib, 10 mg qd ($n = 212$)	Rofecoxib, 25 mg qd ($n = 208$)	Placebo ($n = 110$)
0.5	5.54 ± 1.1	3.09 ± 1.1	5.54 ± 1.4
1.0	9.39 ± 1.3	7.30 ± 1.3	8.8 ± 2.0
1.5	14.95 ± 1.6	11.77 ± 1.5	11.33 ± 2.3
2.0	18.70 ± 1.8	15.33 ± 1.7	13.87 ± 2.5
3.0	21.65 ± 2.0*	19.75 ± 1.8*	15.49 ± 2.8
4.0	24.94 ± 1.9**	22.79 ± 1.9**	16.73 ± 2.6
5.0	26.64 ± 2.0***	25.16 ± 2.0***	16.87 ± 2.7
6.0	28.97 ± 2.0***	27.97 ± 2.0***	16.48 ± 2.8

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs placebo.

In the ITT population, the percentage of patients with onset of analgesia was significantly higher relative to placebo from 4 h for both valdecoxib (55%) and rofecoxib (56%) compared with placebo (40%); $P = 0.015$ vs valdecoxib; $P = 0.008$ vs rofecoxib.

Median time to first onset of analgesia in the ITT population including all participants was shorter with both valdecoxib (3 h; 95% CI: 2.0, 4.0) and rofecoxib (3 h; 95% CI: 2.0, 3.0) compared with placebo 4 h (95% CI: 2.0, >6.0; $P = 0.104$ vs valdecoxib; $P = 0.036$ vs rofecoxib) (Table IV).

SAFETY

One serious adverse event was reported about 8 days into a 2-week extension of this study: a case of cardiac failure in a male patient, aged 81 years, taking valdecoxib. The event was considered severe and required hospitalization. The patient had a history of coronary artery disease, and had discontinued furosemide 2 months prior to the study without his cardiologist's advice. The investigator believed that there was a reasonable possibility that the events were related to a combination of the patient discontinuing his cardiac medication in July 2002 and the initiation of valdecoxib treatment.

Discussion

An analgesic model has been developed that represents a paradigm shift for the study of OA. OA response to

Table IV
Percent incidence of onset of analgesia, defined as a 25% PI reduction from baseline, during the first 6 h in the ITT population

Time (h)	Valdecoxib, 10 mg qd ($n = 212$)	Rofecoxib, 25 mg qd ($n = 208$)	Placebo ($n = 110$)
1.0	29	25	28
2.0	46	46	39
3.0	50	54*	41
4.0	55*	56**	40
5.0	56*	60**	42
6.0	58*	66***	43

$^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs placebo.

therapy can be considered using two different models: the classic OA study model is a disease management model that focuses on chronic care of a chronic disease, with long-term outcome assessments. A complementary model, as described in this study, focuses on OA flare, and is an acute pain model in which onset of analgesia is the primary outcome target. This latter model is clinically relevant because many patients with OA are treated primarily during periods of flare. It has been suggested that NSAIDs should be used for the shortest duration needed, which may increase intermittent use; accordingly, rapid onset of action would be especially beneficial. Such patients are seeking rapid relief from an acute exacerbation of chronic OA pain; repeated delays in pain relief may lead to peripheral and central sensitization, and a worsening of chronic pain[2].

In the present study, the analgesic model of OA flare allowed separation in PI reductions from placebo with two COX-2 specific inhibitors, valdecoxib 10 mg and rofecoxib 25 mg, known to have analgesic activity in OA with the ability to estimate median time to onset at 30 min intervals. A significant difference vs placebo in PI reductions from baseline occurred on day 1 as early as 3 h after the first dose of treatment. In a post hoc analysis, the incidence of patients with onset of analgesia with walking (defined as a 25% reduction in PI from baseline) was significantly higher after 4 h postdose for valdecoxib or rofecoxib compared with placebo. The median time to first onset of analgesia in the assessable population was significantly shorter for both active treatments (2 h) compared with placebo (4 h).

A substantial placebo response was noted, especially in the first 3–4 h (Fig. 4). A high placebo response rate is also typically seen in OA studies of longer duration that focus on chronic disease management. The onset times for differences in PID VAS for valdecoxib and rofecoxib vs placebo in this study are substantially longer than observed with valdecoxib 40 mg (30 min) and rofecoxib 50 mg (45 min) in oral surgery acute pain trials[6,7]. This marked difference in onset of response in acute dental pain and pain associated with the OA flare may be due to differences in the etiology of pain in the two entities, or differences between the OA and dental pain models.

Other acute pain models assessing analgesic onset with COX-2 specific inhibitors in OA of the knee have recently been described[16,17]. In the present model, treatment commences following a period of OA flare, and patients assess their PI VAS during the first 6 h following medication on day 1. Each pain assessment is made following a 10-min walk on a flat surface. End points during the first 6 h postdose are time-specific PID VAS and SPID-6. In another analgesic model[16], eligible patients are required to have pain in their target knee of $\geq$50 mm VAS after walking 20 paces on a flat surface. The primary end point was PID VAS at 3 and 5 h after the first dose of study medication. Results showed that PID VAS at 3 and 5 h was significantly greater in patients randomized to lumiracoxib 400 mg (19.8 mm) compared with those taking placebo (13.4 mm; $P = 0.004$).

In a different model[17], onset of symptom relief was evaluated in patients with OA of the knee in flare at 4 h after the first dose of treatment, and daily over 6 days, using a categorical scale, Patient Global Assessment of Response to Therapy (PGART). In addition, reduction in pain with walking on a flat surface was assessed using WOMAC VAS from Question 1 of the WOMAC Pain Scale from 28 h after the first dose of treatment, and daily over 6 days. Results have been presented in two identically designed studies of patients randomized to rofecoxib 12.5 mg, the nonspecific NSAID nabumetone 1000 mg, or placebo. From 4 h on day 1 to day 6, a significantly greater proportion of rofecoxib-treated patients had a PGART response of good or excellent compared with those taking nabumetone or placebo ($P < 0.001$). Reduction in pain VAS with walking on a flat surface was also significantly greater with rofecoxib (−27.4) compared with nabumetone (−21.6) and placebo (−14.0; $P < 0.001$) from 28 h on day 1 to day 6.

An important aspect of the present analgesic model is that patients with knee OA flare assessed their pain VAS following a prescribed 10-min walk. This walk is designed to reflect a common, ''real world'', function-oriented activity, which typically causes knee OA joint pain. However, a potential confounder in the present trial was the lack of control for the rate of walking. As patients experience increasing pain, they may compensate by walking more slowly. A slower walk may reduce pain, thereby decreasing patients' assessment of pain VAS. Thus, future study designs may be improved by accounting for patients' rate of walking, distance, and length of time walked.

In conclusion, a clinically relevant analgesic model of knee OA flare has been assessed in a study comparing analgesic onset (with walking) with valdecoxib 10 mg qd, rofecoxib 25 mg qd, and placebo. The model effectively demonstrated PI reductions from baseline vs placebo following a prescribed walk on day 1 as early as 4–5 h after the first dose of treatment. Although other models for pain assessment have been described, this model allows assessment of pain relief responses within hours rather than days or weeks when evaluating analgesic efficacy in OA.

Acknowledgments

The dedicated efforts of Ms. Michele Sawicki, Arthritis Translational Research Program Assistant, in manuscript preparation and processing are deeply appreciated.

References

1. Physician Drug & Diagnosis Audit (PDDA) from Verispan, LLC, 2003.
2. Samad TA, Moore KA, Sapirstein A, Billet S, Allchorne A, Poole S, *et al*. Interleukin-1beta-mediated induction of COX-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature 2001;410:471–5.
3. Goldstein DJ, Wang O, Todd LE, Gitter BD, DeBrota DJ, Iyengar S. Study of the analgesic effect of lanepitant in patients with osteoarthritis pain. Clin Pharmacol Ther 2000;67:419–26.
4. Daniels SE, Desjardins PJ, Talwalker S, Recker DP, Verburg KM. The analgesic efficacy of valdecoxib vs oxycodone/acetaminophen after oral surgery. J Am Dent Assoc 2002;133:611–21.
5. Data on file, Pfizer Inc.
6. Fricke J, Varkalis J, Zwillich S, Adler R, Forester E, Recker DP, *et al*. Valdecoxib is more efficacious than rofecoxib in relieving pain associated with oral surgery. Am J Ther 2002;9:89–97.
7. Christensen K, Cawkwell G. Valdecoxib versus rofecoxib in acute postsurgical pain: results of a randomized controlled trial. J Pain Symptom Manage 2004;27:460–70.
8. Makarowski W, Zhao W, Bevirt T, Recker D. Efficacy and safety of the COX-2 specific inhibitor valdecoxib in the management of osteoarthritis of the hip: a

randomized, double-blind, placebo-controlled comparison with naproxen. Osteoarthritis Cartilage 2002;10: 290–6.
9. Bensen W, Weaver A, Espinoza L, Zhao WW, Riley W, Paperiello B, *et al*. Efficacy and safety of valdecoxib in treating the signs and symptoms of rheumatoid arthritis: a randomized, controlled comparison with placebo and naproxen. Rheumatology (Oxford) 2002;41:1008–16.
10. Camu F, Beecher T, Recker DP, Verburg KM. Valdecoxib, a COX-2-specific inhibitor, is an efficacious, opioid-sparing analgesic in patients undergoing hip arthroplasty. Am J Ther 2002;9:43–51.
11. FDA Public Health Advisory, http://www.fda.gov; April 7, 2005
12. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
13. Steinbrocker O, Traeger C, Batterman R. Therapeutic criteria in rheumatoid arthritis. JAMA 1949;140: 659–62.
14. Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987;65:85–9.
15. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
16. Wittenberg RH, Schell E, Krehan G, Maeumbaed R, Runge H, Schluter P, *et al*. First dose analgesic effect of the cyclo-oxygenase-2 selective inhibitor lumiracoxib in osteoarthritis of the knee: a randomized double-blind, placebo-controlled comparison with celecoxib (NCT00267215). Arthritis Res Ther 2006;8(2):R35 [Epub ahead of print].
17. Weaver AL, Messner RP, Storms WW, Polis AB, Najarian DK, Petruschke RA, *et al*. Treatment of patients with osteoarthritis with rofecoxib compared with nabumetone. J Clin Rheumatol 2006;12:17–25.